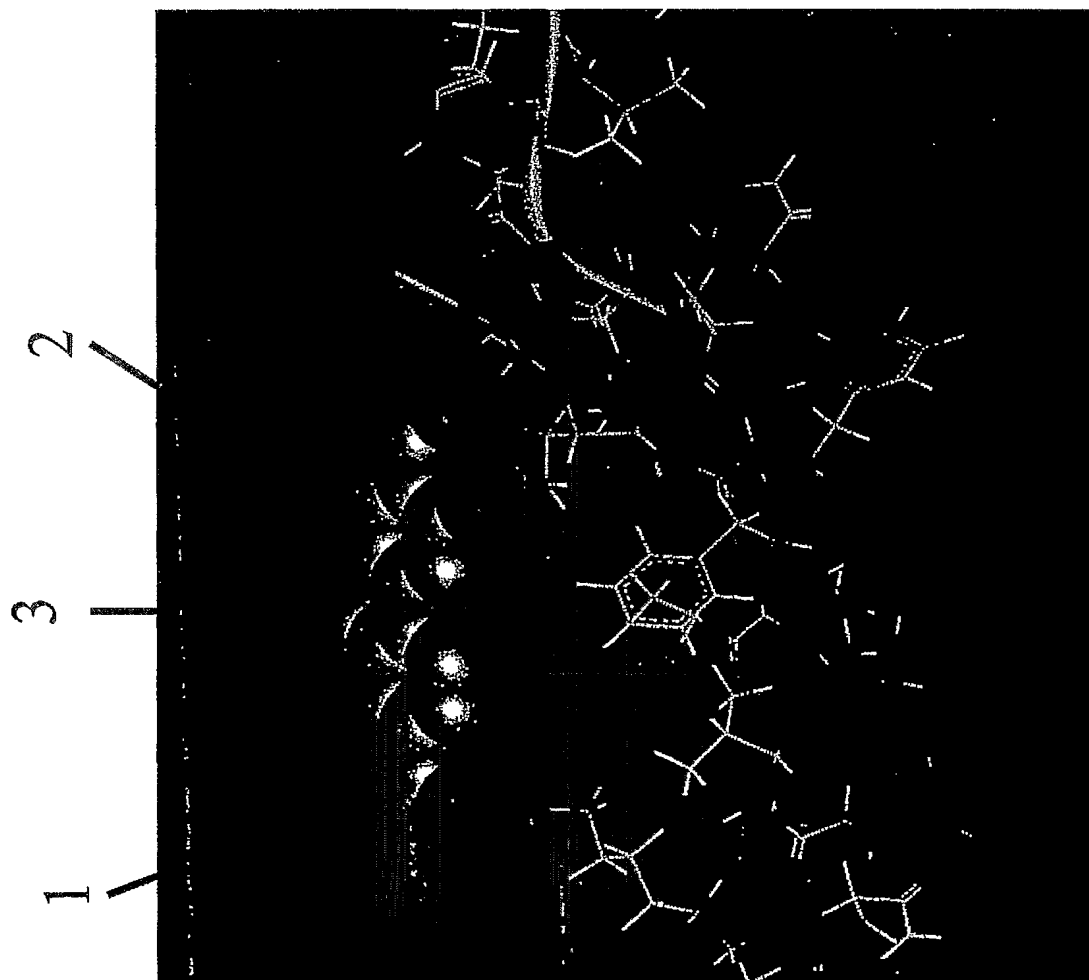


Chemical Approach to Combinatorial Discovery Of β -sheet-Breaking Small Molecules



- 1 – Helix stabilization by selective electrostatic interactions
- 2 – Helix stabilization via interaction with the rigid hydrophobic scaffold
- 3 – Combinatorially varied substituents

FIGURE 1

"Morphomer" concept

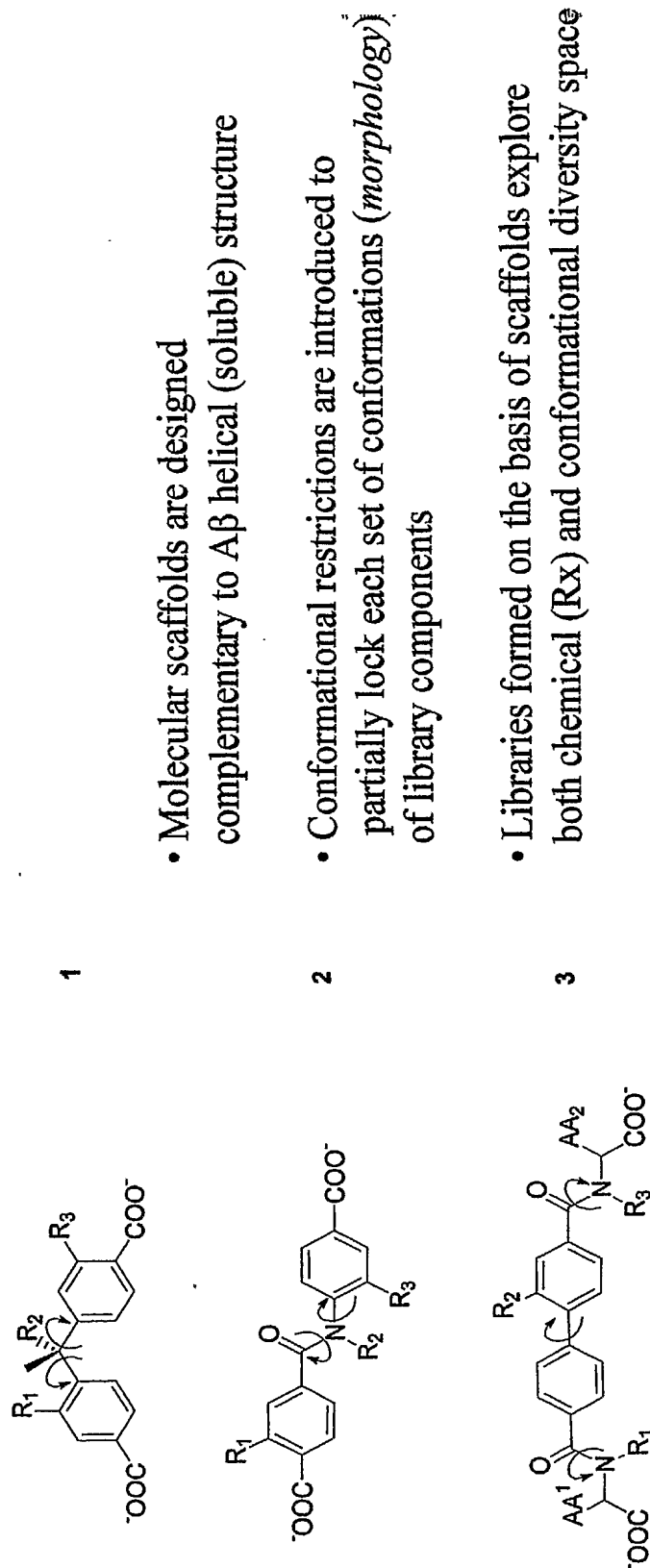


FIGURE 2

Molecular Adaptation of Morphomers to the Target Leads to Formation of Stronger Complexes

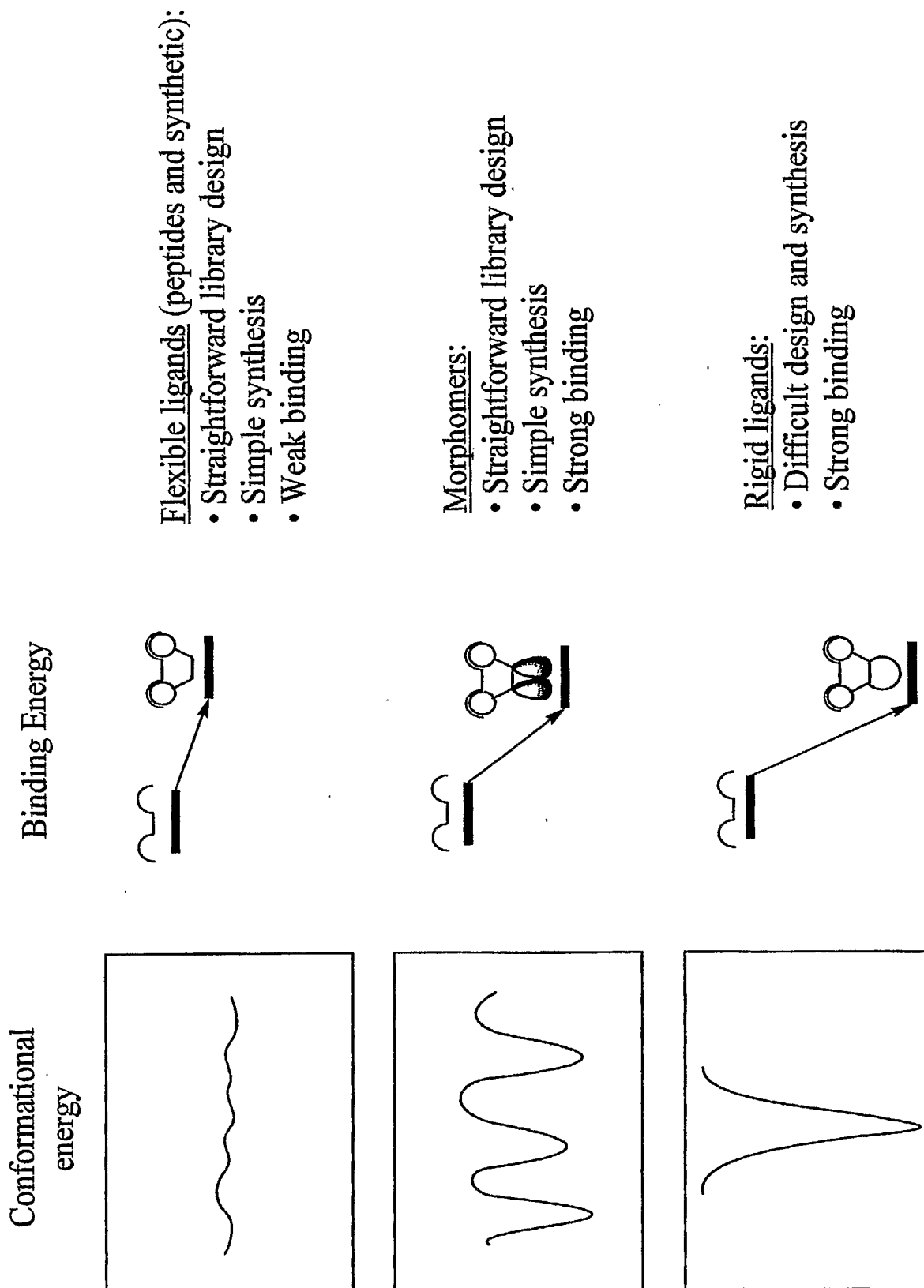
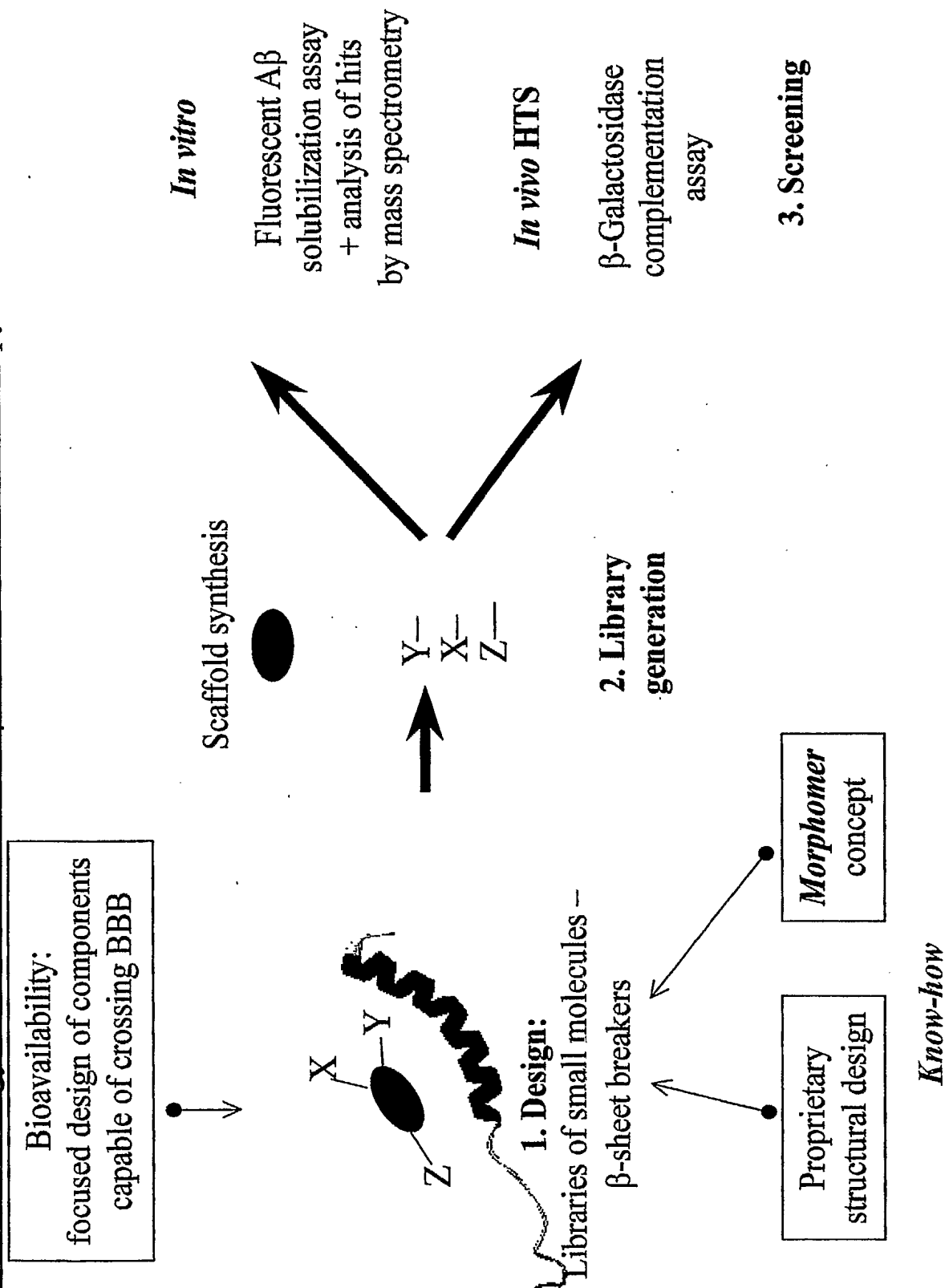


FIGURE 3

FIGURE 4

General Strategy of Small Molecules – β -Sheet breakers for Therapy of Alzheimer's Disease



Screening of Small Molecules for A β Solubilization Activity

In vitro

- **Fluorescent Assay:**

A β fiber stained with Thioflavin T solubilization/depolymerization is monitored by fluorescence decrease

- **Mass spectrometry assay:**

Complexes of amyloid with small molecules are detected and characterized by MS

Hits are fully structurally characterized using regiochemical tagging techniques (*provisional patent application filed*)

In vivo

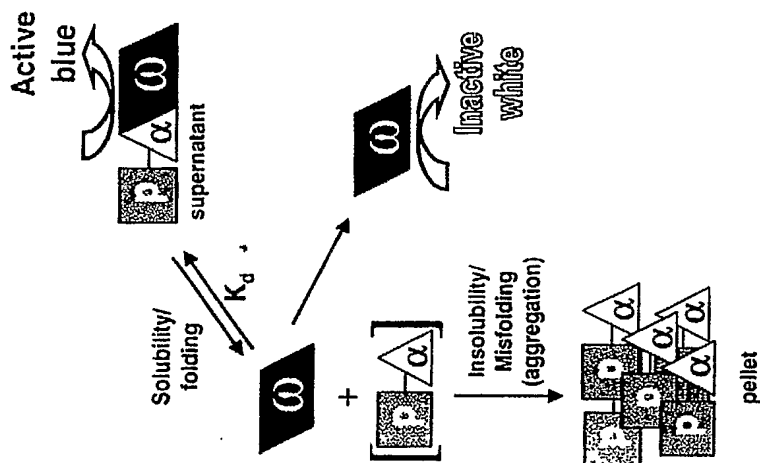


FIGURE 5
in vivo solubilization assay for A β
(W.C. Wigley, et al.
Nature Biotechnol. 2001, 19, 131-136)

Figure 6

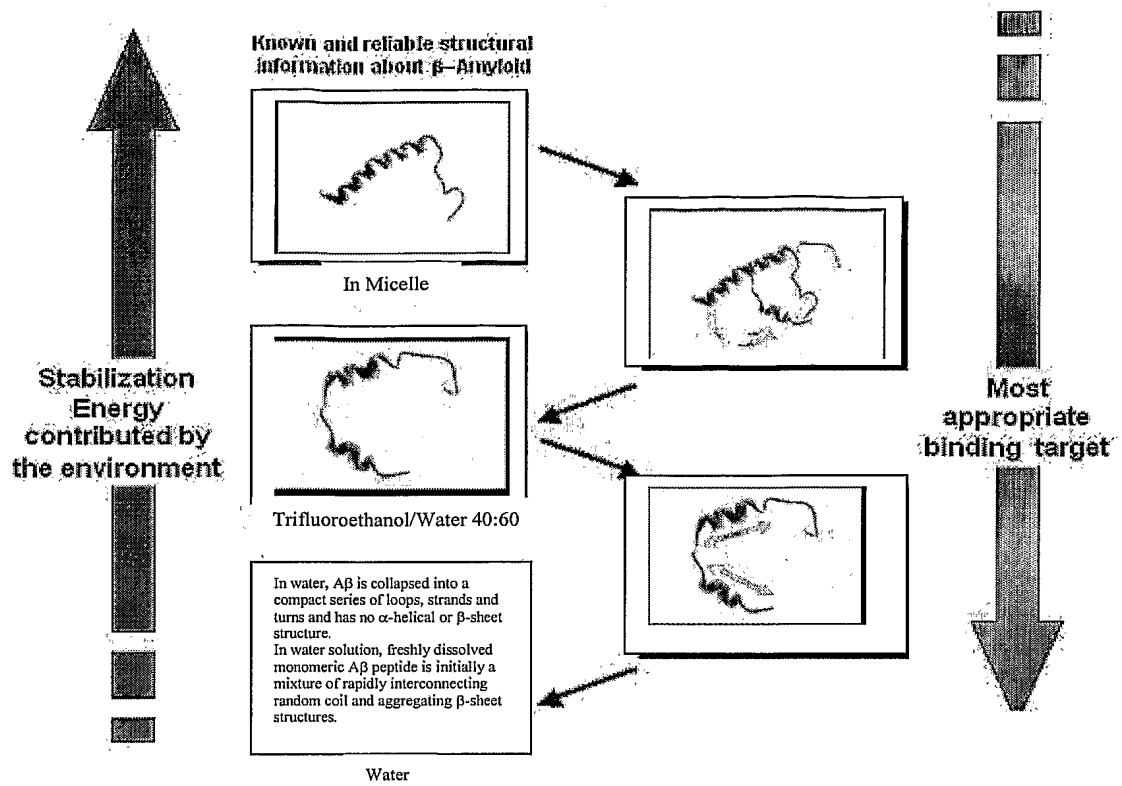


Figure 7

Molecular Design

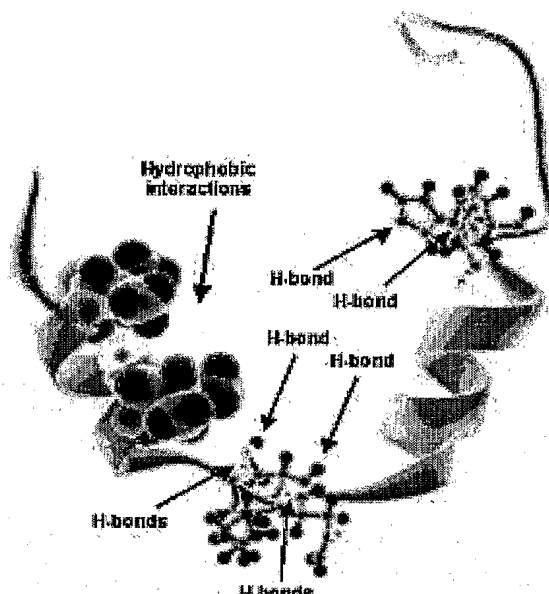
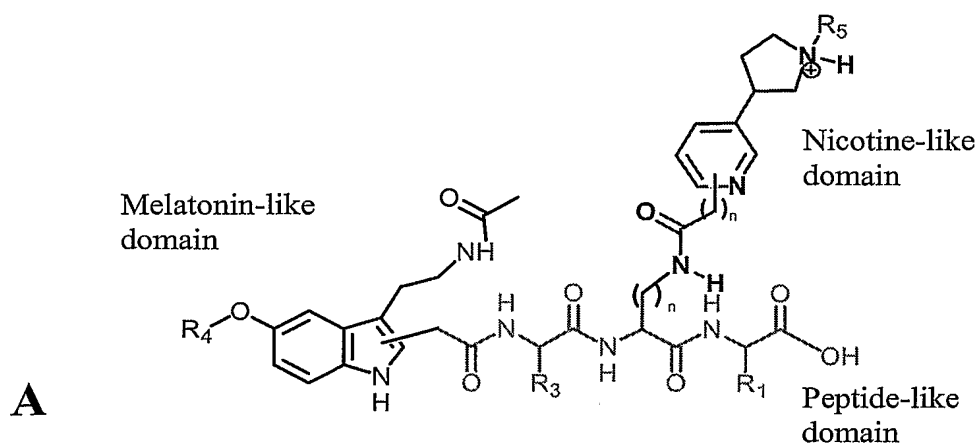


Figure 8



B

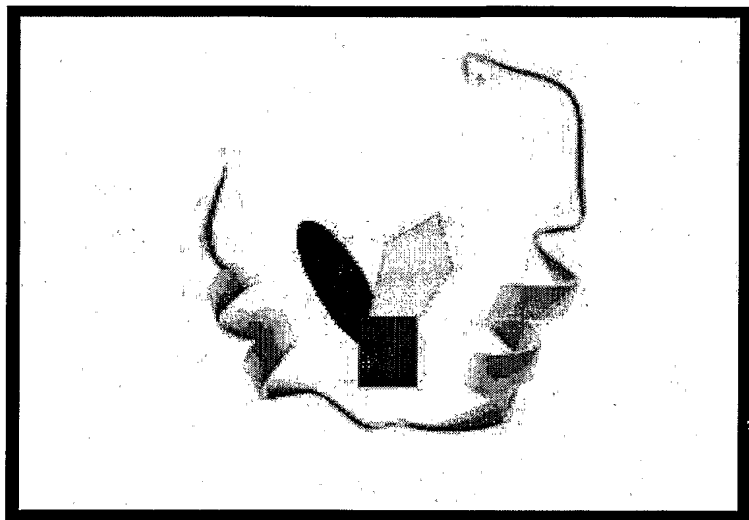


Figure 9

